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Clinical determinants of the 6-Minute Walk Test in bronchiectasis

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Summary
Background: The 6-Minute Walk Test (6MWT) is a widely used measurement of functional exercise capacity in chronic lung disease. While exercise intolerance has been identified in patients with bronchiectasis, the clinical determinants of the 6MWT in this population have not been examined. The aim of this study was to 1) establish the relationship between the 6-Minute Walk Distance (6MWD), disease severity and Health-Related Quality of Life (HRQOL) and 2) identify predictors of exercise tolerance in adults with bronchiectasis.
Methods: The 6MWT was performed in 27 patients with bronchiectasis (mean [SD] FEV_1 73.9% predicted [23.4]). Disease severity was assessed using spirometry and HRCT scoring while HRQOL was evaluated using the St George's Respiratory Questionnaire (SGRQ) and the Short-Form 36 (SF-36). The relationships were evaluated using correlation and multiple regression.
Results: The 6MWD correlated positively with FVC ($r = 0.52$, $p < 0.01$), generations of bronchopulmonary divisions ($r_s = 0.38$, $p < 0.05$) and SF-36 physical summary ($r = 0.71$, $p < 0.001$) while a negative correlation was observed between all domains of the SGRQ (all correlations $r > 0.5$, $p < 0.001$). Multiple regression analysis indicated that the SGRQ activity, symptom scores and generations of bronchial divisions involved were identified as independent predictors of the 6MWD, explaining 76% of the variance.

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Conclusions: Measures of HRQOL demonstrated a stronger association with the 6MWD compared to physiological measures of disease severity in patients with predominantly mild to moderate bronchiectasis.

Introduction

Bronchiectasis not attributable to Cystic Fibrosis (CF) is a chronic respiratory condition, characterised by cough and sputum production[1–3] together with physical fatigue and reduced exercise tolerance.[4,5] Postulated causes of diminished exercise capacity include dyspnoea secondary to dynamic hyperinflation,[6] altered respiratory mechanics and decreased skeletal muscle bulk.[4,7] However, there has been limited evaluation of physical function in patients with bronchiectasis and the influence of respiratory disease severity and extent of bronchiectasis on exercise capacity is unclear.

The 6-Minute Walk Test (6MWT) is a widely used measure of functional status, as well as being a predictor of prognosis across a multitude of respiratory conditions.[8–12] Although these clinical applications suggest that this simple measurement may also be a reflection of the pulmonary and functional status of patients with bronchiectasis, evaluation of the 6MWT in this population has been limited. While other measures of exercise capacity have been linked to Health-Related Quality of Life (HRQOL),[4] the relationship between the 6-Minute Walk Distance (6MWD) and HRQOL in bronchiectasis is unclear. Furthermore, the role of physiological markers of disease severity or HRQOL as clinical predictors of the 6MWD in patients with bronchiectasis has not been evaluated. In this pilot study, we aimed to 1) examine the relationship between lung disease severity, HRQOL and the 6MWD and 2) to identify those clinical variables predicting functional exercise capacity in a group of patients with bronchiectasis.

Methods

Subjects

This is a within-subject correlational study of a group of adults who were recruited from an outpatient clinic of a tertiary hospital for a prospective evaluation of gastro-oesophageal reflux in non-CF bronchiectasis. A diagnosis of bronchiectasis was confirmed by High-Resolution Computed Tomography (HRCT). All participating subjects were non-smokers. Exclusion criteria were a concurrent diagnosis of Chronic Obstructive Pulmonary Disease (COPD), based on clinical presentation, including smoking history[13] together with a demonstration of emphysema on HRCT. Patients were also excluded if they had a clinical history of asthma and/or an increase in FEV_1 by 200 ml or greater than or equal to 12% following bronchodilator therapy[14] or confirmation of interstitial lung disease based on diagnostic guidelines.[15] A total of five patients were prescribed bronchodilator therapy (salbutamol) while five were using long-term antibiotics at the time of the study. Clinical stability was required for all patients and was defined as the absence of clinical deterioration beyond normal daily variations without increasing need for usual or rescue medication during the four weeks prior to evaluation.[16] Approval for this project was obtained from institutional HREC and written informed consent was obtained from each patient.

Procedure

The extent of bronchiectasis according to HRCT, measured within 12 months of participation in the study was evaluated by a consultant radiologist using the scoring system proposed by Bhalla et al.[17] The aetiology of bronchiectasis was determined through review of clinical records detailing investigations of predisposing factors, including immunoglobulin levels with subclasses, ciliary function (primary ciliary dyskinesia), Allergic Bronchopulmonary Aspergillosis (ABPA) and post-infective origin. In the event of no identifying aetiology, the cause was classified as idiopathic. Gender, age and Body Mass Index (BMI) were collated for each patient. Lung function tests (spirometry) using the Medgraphics Corporation Lung Function testing system (Minnesota, USA) and Software Breeze Suite V6.2A and 6.2C were performed on the day prior to exercise testing according to the ATS guidelines.[18]

HRQOL was recorded using the St George's Respiratory Questionnaire (SGRQ)[19] and the Short-Form 36 (SF-36).[20] The SGRQ is a disease-specific tool composed of 50 items assessed by three subscales, symptoms, impact and activity as well as a total score.[21] The score of each domain as well as the total score is calculated as a function of the item scores, with lower scores indicating better HRQOL and higher scores indicating worse HRQOL, ranging from 0 to 100. The SGRQ has been validated in patients with bronchiectasis.[4] The SF-36 is a generic measure which evaluates HRQOL over eight domains.[20] Based on the scores in each of these domains, physical and mental summary scores were calculated. Poor HRQOL is indicted by a lower score on the SF-36.

Each patient completed two 6MWTs according to a standardised protocol.[22] The test was conducted along an enclosed 30 m corridor and patients were instructed to walk at their own pace but to cover as much ground as possible within 6 min. Standardised encouragement was provided during the test. Oxygen saturation (SpO_2) was monitored throughout the walk. The greatest distance out of the two tests was recorded as the 6MWD.

Data management

Statistical analyses were performed using SPSS for Windows version 15.0. Data are expressed as means (SD). The relationship between variables was examined using Pearson's

correlation coefficient or Spearman's rho depending on the distribution of the data. Differences between groups based on gender were analysed using Student's *t*-test. Multivariate linear regression analysis was conducted to determine predictors of the 6MWD, with variables found to be significant at $p < 0.05$ on univariate analysis included in the model. Where multi-collinearity was apparent, the variable with the highest significance level on univariate analysis was included. Statistical significance was accepted at an alpha <0.05.

Results

Patient characteristics

A total of 27 patients (16 female) with bronchiectasis participated in this study. Demographic data and baseline lung function are outlined in Table 1, with only two patients awaiting lung transplantation at the time of the study. The aetiology of bronchiectasis was attributed to six possible causes. These included childhood or adult illnesses including pertussis, measles or pneumonia in 13 patients (46.7%). Idiopathic bronchiectasis was evident in 10 patients (33%), while primary hypogammaglobulinaemia was the identified source in two patients (7%). Young's syndrome, ABPA and diffuse panbronchiolitis were underlying aetiologies in one patient each.

Table 2 shows the severity of bronchiectasis based on HRCT scoring.[17] The severity of bronchiectasis was predominantly mild to moderate (93%) with mild peribronchial thickening in all patients. While the majority of patients (70%) had at least six bronchopulmonary segments involved, evidence of mucus plugging was present in only 44% of subjects. Most patients demonstrated involvement of at least the 5th generation of bronchial division (93%). Accompanying collapse or consolidation was found in the subsegmental or segmental region in 56% of patients.

Fig. 1 depicts a histogram of the 6MWD, which ranged from 300 to 750 m. No patient required ambulatory oxygen therapy (i.e. $SpO_2 < 85\%$ during the test). The mean (SD) SGRQ total score was 41.5 (16.8). The mean (SD) SF-36 physical and mental summary scores were 38.5 (11.2) and 48.3 (8.7) respectively. There was a wide range of HRQOL scores for both SGRQ and SF-36, with evidence of optimal HRQOL (lowest possible score) according to the SGRQ symptom and activity scores in some patients. There was a significant correlation between all three components of the SGRQ (symptoms, activity and impact) and the SF-36 physical summary ($p < 0.05$ for all correlations).

Table 1 Demographic data for subjects with bronchiectasis ($n = 27$).

Demographic factor	Mean (SD)	95% CI
Age (years)	54.4 (13.8)	40.8—74.7
BMI (kg/m^2)	26.6 (5.8)	21.8—39.4
FEV_1 (L)	2.3 (0.9)	1.6—4.0
FEV_1% predicted	73.9 (23.4)	52.3—108.5
FVC (L)	3.4 (1.1)	2.8—5.3
FVC % predicted	89.4 (20.2)	78.3—126.9
6MWD (m)	547.4 (115.8)	430.5—725.6

BMI = Body Mass Index; FEV_1 = Forced Expiratory Volume in one second; FVC = Forced Vital Capacity; 6MWD = 6-Minute Walk Distance.

Table 2 Severity of bronchiectasis according to HRCT.

HRCT scoring classifications		*N* (%)
Bronchiectasis severity	Mild	15 (56)
	Moderate	10 (37)
	Severe	2 (7)
Peribronchial thickening	Mild	27 (100)
Extent of bronchiectasis	1—5	8 (30)
	6—9	9 (33)
	>9	10 (37)
Extent mucus plugging	Absent	15 (56)
	1—5	10 (37)
	6—9	2 (7)
Sacculations	Absent	25 (93)
	1—5	2 (7)
Generations	Up to 4th	2 (7)
	Up to 5th	10 (37)
	Up to 6th	15 (56)
Bullae	Absent	26 (96)
	>5	1 (4)
Emphysema	Absent	27 (100)
Collapse/consolidation	Absent	12 (44)
	Subsegmental	8 (30)
	Segmental/lobar	7 (26)

Relationships between clinical features and exercise tolerance

Females had poorer exercise tolerance compared to males on the 6MWT (mean difference of 96 m, 95% CI -182.1 to -9.1 m, $p = 0.023$). There was no relationship between the 6MWD, age or BMI (Table 3). Spirometric measures of disease severity correlated moderately with the 6MWD, suggesting that a higher exercise tolerance was present in those with

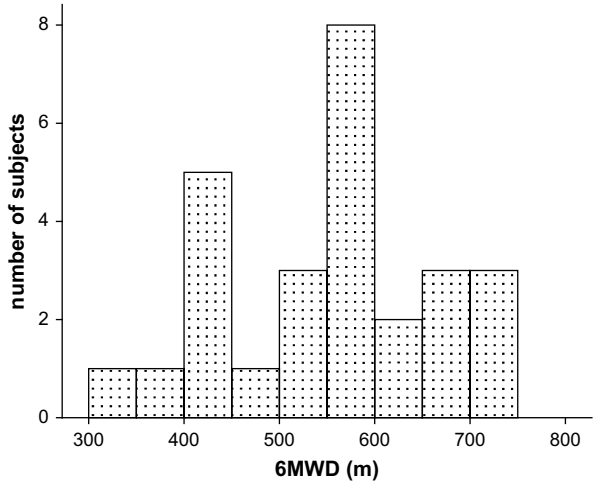

Figure 1 Histogram demonstrating the distribution of the 6MWD.

Table 3 Correlations between 6MWD, clinical variables and HRQOL.

	6MWD[a]	*p* value
Age (years)	−0.324	$p = NS$
BMI (kg/m^2)	−0.241	$p = NS$
FEV_1 % pred	0.485	$p = 0.035$
FVC % pred	0.513	$p = 0.006$
Severity of bronchiectasis	−0.024	$p = NS$
Extent of bronchopulmonary segments involved	−0.34	$p = 0.083$
Extent of mucus plugging	0.086	$p = NS$
Sacculations	−0.061	$p = NS$
Generations of bronchial divisions involved	0.382	$p = 0.049$
Collapse/consolidation	0.039	$p = NS$
SGRQ symptom score	−0.642	$p < 0.000$
SGRQ activity score	−0.768	$p < 0.000$
SGRQ impact score	−0.678	$p < 0.000$
SGRQ total score	−0.820	$p < 0.000$
SF-36 physical summary score	0.709	$p < 0.000$
SF-36 mental summary score	−0.059	$p = NS$

[a] Data expressed as Pearson's r or Spearman's rho; NS = Non-significant, 6MWD = 6-Minute Walk Distance, BMI = Body Mass Index; FEV_1 = Forced Expiratory Volume in one second; FVC = Forced Vital Capacity; SGRQ = St George's Respiratory Questionnaire, SF-36 = Short-Form 36.

less airway obstruction (Table 3). However, only a weak relationship between generations of bronchial divisions and the 6MWD was demonstrated, with a higher 6MWD in those with more generations involved. No other relationship between severity of bronchiectasis and the 6MWD was evident. The 6MWD was strongly associated with all domains of the SGRQ and the SF-36 physical summary (Table 3) with the strongest relationships exhibited with SGRQ activity score and total score. Overall, exercise tolerance demonstrated a stronger correlation to HRQOL than physiological measures of lung function or disease severity.

A multivariate linear regression analysis was completed using those factors found to be significant by univariate analysis, including FVC% predicted, generations of bronchial divisions and SGRQ symptom, activity and impact scores. The SGRQ symptom and activity scores and generations of bronchial divisions were identified as independent predictors of the 6MWD, in total explaining 76% of the variance. A lower 6MWD was associated with higher SGRQ symptom and activity scores (which indicated worse HRQOL) and fewer generations of bronchial divisions on HRCT.

Discussion

To our knowledge, this is the first study to describe the relationship between the 6MWD and clinical variables including disease severity and HRQOL in a group of patients with predominantly mild to moderate bronchiectasis. The 6MWD demonstrated a stronger relationship with HRQOL domains compared to physiological measures of lung disease severity and limited association with structural abnormalities of bronchiectasis. HRQOL measures incorporating symptom severity and activity limitations were stronger independent predictors of the 6MWD compared to physiological parameters.

Increased sputum production and progressive airflow obstruction have been suggested determinants of reduced exercise tolerance in bronchiectasis.[7,23] Physiologically, this is supported by evidence of expiratory flow limitation, which indicates that dynamic hyperinflation and increased work of breathing are responsible for the strong relationship between dyspnoea and maximal power output (WRmax).[6] Evidence of airflow obstruction measured using FEV_1 and FVC associated with a reduced 6MWD in this study lends support to this concept and is consistent with a lowered aerobic capacity and reduced maximal ventilation in 50% of children with bronchiectasis.[24]

Despite this moderate relationship, spirometric measures of disease severity were not independent predictors of exercise tolerance. This is likely to be due to the fact that the majority of subjects had relatively well preserved lung function. It also suggests that other factors independent of lung function may influence exercise capacity in this patient population; for example skeletal muscle dysfunction. Alterations in peripheral muscle structure with associated impaired oxidative capacity are key contributors to diminished exercise tolerance in patients with COPD.[25,26] Exertional dyspnoea leads to the adoption of sedentary lifestyles in patients with COPD, imposing a cycle of progressive inactivity, deconditioning and peripheral muscle disuse.[27,28] While these systemic effects may be reflected by the physical fatigue reported in patients with bronchiectasis,[3,5] peripheral muscle function in this population has not yet been evaluated.

The strong association between the 6MWD, all components of the SGRQ and SF-36 physical summary is consistent with a previous study examining the relationship between exercise capacity and HRQOL in bronchiectasis.[4] In this study of 111 patients, the distance walked on the Incremental Shuttle Walk Test (ISWT) moderately correlated with SGRQ symptom ($r = 0.30$) and was strongly related to SGRQ activity ($r = 0.65$) and total scores ($r = 0.56$).[4] The SGRQ symptom domain is focused on the frequency, severity and duration of signs and symptoms synonymous with bronchiectasis while the activity domain concentrates on the physical restrictions and impairment secondary to respiratory symptoms.[19,21] Exertional dyspnoea and physical fatigue secondary to chronic infection are recognised as contributing factors to diminished physical function in bronchiectasis.[2,3,29] On this basis, it was not unexpected that the SGRQ activity score was a predictor of the 6MWD in this study. However, our study also supports the view that respiratory signs and symptoms including cough, sputum, wheezing and number of acute exacerbations are clinically relevant when evaluating physical capacity in patients with mild to moderate bronchiectasis.

The association between structural lung disease determined by HRCT and exercise tolerance appears to be limited with only generations of bronchial division involved a predictor of the 6MWD. This absence of relationship between HRCT findings and maximal exercise capacity has been previously described[30] and the similar observation in this study may be due to the inclusion of a small number of patients (7%) with severe bronchiectasis. The extent of

bronchiectasis also appears to have limited influence on HRQOL or respiratory symptoms,[5,31,32] with significant correlations restricted to patients with severe and extensive bronchiectasis.[31] Although a weak predictor of the 6MWD in this study, the association of a greater 6MWD in those with more generations of bronchial divisions affected should be interpreted with caution. The presence of more than six generations affected in 57% of patients included in this study may account for this result and requires further clarification in a larger group of patients. In addition, it is possible that patients with more extensive bronchiectasis have been advised to incorporate more exercise as part of their disease management and therefore have a greater exercise capacity compared to those with milder disease.

The strong relationship between the 6MWD and HRQOL in this study implies that strategies to address diminished exercise capacity through formalised exercise programs in bronchiectasis may have a similar positive impact on HRQOL. This effect has been consistently demonstrated following exercise training in patients with COPD.[33] While international guidelines for pulmonary rehabilitation support the inclusion of patients with bronchiectasis,[34,35] there is limited evidence supporting exercise training. A recent study has documented improvements in ISWT distance in a group of patients with bronchiectasis following lower limb endurance and inspiratory muscle training.[36] However, unlike other populations with respiratory disease, significant improvements in HRQOL were not seen. Further research to confirm the benefits of recommended exercise prescription outlined in pulmonary rehabilitation guidelines for patients with bronchiectasis is required.

This study was limited by the small number of subjects recruited, the majority of whom demonstrated mild to moderate bronchiectasis. For this reason, the results cannot be extrapolated to patients with severe disease. Identification of additional clinical determinants of the 6MWD in patients with bronchiectasis will require a larger cohort of subjects across the disease spectrum.

In conclusion, this preliminary study indicates that the 6MWT provides valuable information of the functional status in a group of patients with mild to moderate bronchiectasis, being dependent on an objective assessment of bronchial divisions involved and a subjective assessment of HRQOL. A stronger relationship between the 6MWD and physical symptoms as detected by HRQOL was evident compared to physiological measures of disease severity. Management strategies to improve exercise tolerance in the form of exercise training have the potential to impact positively on HRQOL in this patient population.

Conflict of interest

The authors have no conflicts of interests.

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